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Case Report

Mitochondrial deformity confined to a single cardiomyocyte in human endomyocardial biopsy specimens: Report of 4 cases

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ABSTRACT

During electron microscopic examination of 156 consecutive human endomyocardial biopsy specimens, we found marked mitochondrial deformity within a single cardiomyocyte in each of 4 specimens. The deformed mitochondria were unevenly distributed, but the deformities were confined to the one cardiomyocyte. Those affected cardiomyocytes were accompanied by nonspecific degenerative changes such as nuclear hypertrophy and/or rarefaction of the myofibrils. Mitochondria in all other cells within the specimens appeared normal. Such an abnormality has never been reported to date. Each of the four cases was diagnosed with a different ailment: post-myocarditis, dilated cardiomyopathy, amyloidosis, and tachycardia-induced heart failure. However, all four cases were accompanied by left ventricular systolic dysfunction at biopsy. The very limited mitochondrial deformation may thus reflect a type of degenerative change that accompanies heart failure.

<**Learning objective:** A marked mitochondrial deformity must have been overlooked to date, which is confined to a single cardiomyocyte in an endomyocardial biopsy specimen. Its etiology is still unknown but may reflect a type of degenerative change that accompanies heart failure.>

Introduction

Mitochondria are the primary source of energy, in the form of ATP, that fuels the contractile apparatus within cardiomyocytes, and are thus essential for the heart's pumping activity. Accumulation of disorganized small mitochondria (mitochondriosis) is observed in a variety of cardiac conditions associated with heart failure, including dilated cardiomyopathy [1] and myocardial hibernation [2]. Changes in mitochondrial fusion and fission proteins have been demonstrated in a rat model of postmyocardial infarction [3], and may be responsible for mitochondriosis, although the significance of these changes to the pathogenesis of heart failure is unclear if they are secondary to metabolic changes. Heart failure is indeed associated with reduced mitochondrial oxidative phosphorylation and production of oxidative stress, but it is unknown whether changes in mitochondrial morphology contribute to the pathogenesis of mitochondrial dysfunction during heart failure [4,5]. Within failing hearts, mitochondria with subtle abnormal morphologies can be observed in most cardiomyocytes, but it is unusual for the abnormality to be confined to a single cardiomyocyte.

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Presentation of the cases

Over a period of 3 years (2013–2015), 156 consecutive endomyocardial biopsy specimens were collected and examined in an electron microscope (H700 or HT7700, Hitachi, Tokyo, Japan) for routine diagnostic purposes at Gifu University School of Medicine, Kizawa Memorial Hospital, Nara Medical College, Yamaguchi University School of Medicine, Nagoya University School of Medicine, Niigata University School of Medicine, and Gifu Heart Center. The specimens were obtained from 80 patients with dilated cardiomyopathy (including post-myocarditis), 34 with hypertrophic cardiomyopathy, 8 with amyloidosis, 8 with mitochondrial cardiomyopathy, 7 with sarcoidosis, 4 with Fabry disease, 4 with hypertensive heart disease, 3 with adriamycin cardiomyopathy, 2 with acute myocarditis, 2 with arrhythmogenic right ventricular cardiomyopathy, 2 with Sjogren's syndrome combined with pulmonary hypertension, 1 with peripartum cardiomyopathy, and 1 with unsustained ventricular tachycardia.

Endomyocardial biopsy specimens were immediately fixed for 4 h in 2.5% glutaraldehyde in 0.1 mol/l phosphate buffer. The specimens were then postfixed in 1% osmium tetroxide for 1 h, dehydrated through graded ethanol and propylene oxide series and embedded in epon. They were sectioned at 0.7-μm thickness (semithin sections) and stained with toluidine blue dye and thereafter thin-sectioned (70 nm) using an ultramicrotome, mounted on plain copper grids, stained with uranyl acetate and lead citrate, and examined by an H700 or HT7700 transmission electron microscope (Hitachi). We counted the number of cardiomyocytes contained in each specimen using toluidine blue-stained semithin sections under a light microscope.

During these examinations, we observed marked mitochondrial deformities within cardiomyocytes. Moreover, the abnormal morphology was unevenly distributed within the cells and showed different patterns of deformity. Notably, in four cases the mitochondrial deformity was confined to a single cardiomyocyte; all the mitochondria in the other cardiomyocytes in each specimen appeared normal. These four cases are presented here.

Case 1

Case 1 was a 91-year-old man admitted to the hospital because of faintness due to pacing failure of his pacemaker. The permanent

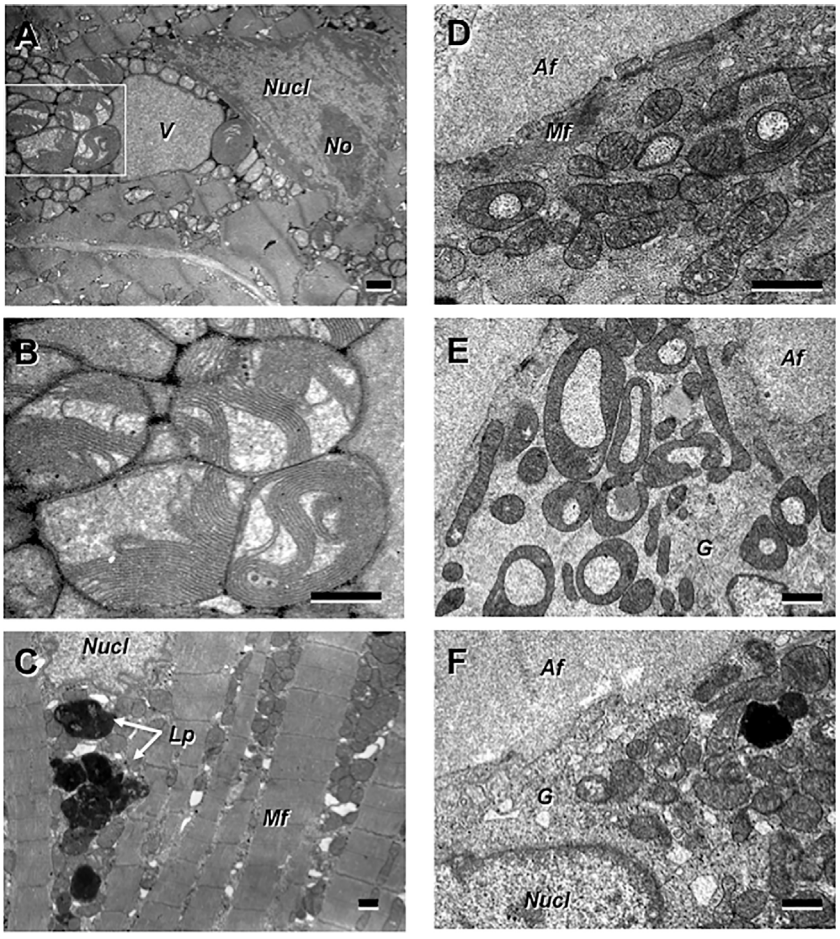

Fig. 1. Electron micrographs of Case 1 (A–C) and Case 2 (D–F). Panels A and B show mitochondria with unusual shapes in one cardiomyocyte; panel B is the highly magnified photograph of the square portion of panel A. Nearly all mitochondria in this cell are abnormal; some are gigantic and have abnormal running cristae or cristae that dissolve. In addition, the nucleus of the cell was hypertrophic, i.e. bizarre shaped with chromatin clumping. All other cardiomyocytes in the specimen had normal mitochondria (C). Panels D and E show amyloid fibrils diffusely distributed in the myocardial interstitium and apparently abnormal mitochondria in one cardiomyocyte. The mitochondria are donut-shaped with glycogen granules in the center, or they are abnormally elongated. In this cell, rarefaction of the myofibrils is apparent due to marked accumulation of glycogen granules. No mitochondrial abnormality was detected in the other cardiomyocytes in the specimen (F).
Af, amyloid fibrils; G, glycogen granules; Lp, lipofuscin; Mf, myofibrils; No, nucleolus; Nucl, nucleus; V, vacuole.
Scale bars, 1 μm.

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